DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Silver Spring, MD 20993

Rachel Henderson, PharmD
Senior Manager, Office of Promotion and Advertising Review
Merck & Co, Inc.
PO Box 1000, UG3BC-10
North Wales, PA 19454-1099

RE: NDA 022117
Saphris® (asenapine) sublingual tablets
MA# 266

Dear Dr. Henderson:

This letter notifies Merck & Co, Inc. (Merck) that the Office of Prescription Drug Promotion (OPDP) of the U.S. Food and Drug Administration (FDA) has become aware of oral statements made by Dr. Armando Favazza, MD, on behalf of Merck, regarding Saphris® (asenapine) sublingual tablets (Saphris) at a lunch presentation on April 26, 2011, submitted as a complaint to the OPDP Bad Ad Program. The speaker's statements misleadingly suggest that Saphris is safe and effective for an unapproved use, for which the drug's labeling lacks adequate direction for use. Thus, this promotional activity misbrands Saphris in violation of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 352(f)(1), (n).

Background

Below is a summary of the indication, and the most serious and most common risks associated with the use of Saphris.[1] The FDA-approved product labeling (PI) for Saphris states the following (in pertinent part; emphasis in original):

> SAPHRIS is indicated for the treatment of schizophrenia. . . .
>
> **Monotherapy**: SAPHRIS is indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder. . . .
>
> **Adjunctive Therapy**: SAPHRIS is indicated with either lithium or valproate for the acute treatment of manic or mixed episodes associated with bipolar I disorder. . . .

The PI for Saphris includes a Boxed Warning regarding increased mortality in elderly patients with dementia-related psychosis. Contraindications for Saphris include known hypersensitivity to the drug or its components. The PI also contains Warnings and Precautions regarding: cerebrovascular adverse events; neuroleptic malignant syndrome;

[1] This information is for background purposes only and does not necessarily represent the risk information that should be included in the promotional activities cited in this letter.

tardive dyskinesia; hyperglycemia and diabetes mellitus; weight gain; orthostatic hypotension and syncope; leukopenia, neutropenia, and agranulocytosis; QT prolongation; seizures; potential for cognitive and motor impairment; and suicide.

The most commonly reported adverse reactions for Saphris (incidence ≥5% and at least twice the rate of placebo) are:

- For Schizophrenia: akathisia, oral hypoesthesia, and somnolence;
- For Bipolar I Disorder (Monotherapy): somnolence, dizziness, extrapyramidal symptoms other than akathisia, and weight increased; and
- For Bipolar I Disorder (Adjunctive Therapy): somnolence and oral hypoesthesia.

Prior Communication

On September 1, 2011, OPDP sent a letter of inquiry (LOI) to Merck to determine the extent of Merck's involvement in the lunch presentation given by Dr. Favazza. OPDP also inquired about the nature of the relationship between Dr. Favazza and Merck. The responses from Merck dated September 15, 2011, and October 14, 2011, indicate that a Merck Peer Discussion Group (PDG) luncheon event was held on April 26, 2011, and the speaker for the event was Dr. Favazza. (b) (4)

Additionally, the response dated October 14, 2011, indicates that Dr. Favazza did not use slides or disseminate materials during the April 26, 2011, PDG event.

Promotion of an Unapproved Use

On April 26, 2011, Dr. Favazza delivered a lunch presentation on Saphris to a group of healthcare professionals at the Anderson Center of Saint John's Health Center in Anderson, Indiana. The presentation was given orally and did not include any slides or handouts. During his presentation, Dr. Favazza indicated that he prescribes Saphris as an adjunctive treatment for major depressive disorder (MDD) just as he might prescribe Abilify, and that it works just as well.[2]

The oral statement made by Dr. Favazza misleadingly suggested that Saphris is safe and effective for use as an adjunctive treatment for MDD. According to its PI, Saphris is only indicated for the treatment of patients with schizophrenia or for the acute treatment of manic or mixed episodes associated with bipolar I disorder, either as a monotherapy or adjunctive treatment with lithium or valproate. Therefore, the oral statement made by Dr. Favazza misbrands the drug by suggesting a new "intended use" for Saphris for which the PI lacks adequate directions for use.[3]

[2] Abilify is an atypical antipsychotic with several approved indications, including the adjunctive treatment of major depressive disorder.
[3] *See* 21 CFR 201.100(c)(1); 21 CFR 201.128.

Conclusion and Requested Action

For the reasons discussed above, the oral statements made by Dr. Favazza on behalf of Merck misbrand Saphris in violation of the FD&C Act, 21 U.S.C. 352(f)(1), (n).

OPDP requests that Merck immediately cease violative promotional activities/materials for Saphris, such as those described above. Please submit a written response to this letter on or before March 13, 2012, stating whether you intend to comply with this request, listing all promotional activities/materials (with the 2253 submission date) for Saphris that contain violations such as those described above, and explaining your plan for discontinuing use of such violative materials. Please direct your response to the undersigned at the **Food and Drug Administration, Center for Drug Evaluation and Research, Office of Prescription Drug Promotion, Division of Professional Promotion, 5901-B Ammendale Road, Beltsville, Maryland 20705-1266** or by facsimile at (301) 847-8444. Please note that the Division of Drug Marketing, Advertising, and Communications (DDMAC) has been reorganized and elevated to the Office of Prescription Drug Promotion (OPDP). OPDP consists of the Immediate Office, the Division of Professional Promotion (DPP) and the Division of Direct-to-Consumer Promotion (DDTCP). To ensure timely delivery of your submissions, please use the full address above and include a prominent directional notation (e.g. a sticker) to indicate that the submission is intended for OPDP.

In addition, OPDP recently migrated to a different tracking system. Therefore, OPDP letters will now refer to MA numbers instead of MACMIS numbers. Please refer to the MA# 266 in addition to the NDA number in all future correspondence relating to this particular matter. OPDP reminds you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that your promotional materials for Saphris comply with each applicable requirement of the FD&C Act and FDA implementing regulations.

Sincerely,

{See appended electronic signature page}

Jessica N. Cleck Derenick, PhD
Regulatory Review Officer
Division of Professional Promotion
Office of Prescription Drug Promotion

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JESSICA N CLECK DERENICK
02/28/2012